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Thiazide and Thiazide-like Diuretics: An Opportunity to Reduce Blood Pressure in Patients with Advanced Kidney Disease

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Abstract Thiazide and thiazide-like diuretics have been widely used as blood pressure-lowering agents for more than 5 decades. However, their use in patients with advanced chronic kidney disease has been limited and often discouraged. The exact mechanism of how thiazide and thiazide-like diuretics lower blood pressures is still in question. Emerging evidence suggests that thiazides and thiazide-like diuretics are effective as blood pressure-lowering drugs in patients with advanced chronic kidney disease. Review of the literature suggests that physicians should not discard thiazide and thiazide-like diuretics as options for blood pressure management in patients with chronic advanced kidney disease.

Keywords Thiazide · Thiazide-like diuretics · Loop diuretics · Hypertension · Chronic kidney disease · CKD · Blood pressure · Glomerular filtration rate · GFR · Antihypertensive drug therapy

Introduction

Thiazide and thiazide-like diuretics have been used since the 1950s as medications for blood pressure management [1]. Several studies have shown that thiazide and thiazide-like diuretics are effective in reducing blood pressure [2–4]. Antihypertensive drug therapy with diuretics reduces the risk of hypertension-associated morbidity and mortality [3, 5]. The ALLHAT Study suggested that chlorthalidone might be superior to ACE inhibitors (ACEI) or calcium channel blockers in preventing one or more major forms of cardiovascular events [6]. The observations of the ALLHAT study led the JNC-7 Committee to recommend diuretics as a preferred therapy for most patients with hypertension [7]. Since the late 1950s [8] and early 1960s [9], after some studies were published indicating that thiazide and thiazide-like diuretics lose their diuretic and antihypertensive effects when the glomerular filtration rate (GFR) falls below 15 to 20 ml/min/1.73 m^2, many physicians have been avoiding thiazide use in patients with advanced chronic kidney disease (CKD). How do thiazide and thiazide-like diuretics lower blood pressure? Is it all due to natriuresis? Do all thiazide and thiazide-like diuretics have similar efficacy and potency? Do they share a similar mechanism of action? Can we use thiazide and thiazide-like diuretics in patients with advanced CKD for blood pressure control? These issues among others will be addressed in this review.

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Pharmacodynamics and Pharmacokinetics of Selected Thiazide and Thiazide-Like Diuretics

Thiazide and thiazide-like diuretics inhibit the NaCl cotransporter (NCC) in the distal convoluted tubule [10, 11], which is responsible for 5 % to 7 % of the total sodium reabsorption. Thiazide and thiazide-like diuretics were derived from the acetazolamide molecule, a carbonic anhydrase inhibitor, with weak diuretic properties. They both have sulfonamide groups in their basic chemical structure that interact with the carbonic anhydrase enzyme, but thiazides are characterized by having a unique benzothiadiazine dioxide scaffold integrated in their chemical structure. Thiazide and thiazide-like diuretics have been shown to increase urine Na excretion significantly and to lower blood pressure in NCC knockout mice, indicating that NCC is not the only target of thiazide and thiazide-like diuretics in vivo [12, 13].

Hydrochlorothiazide (HCTZ): the most widely used thiazide drug belongs to the benzothiadiazine class. The pharmacological half-life can reach up to 15 h. However, with long-term use [14], once daily dosing lowers blood pressure for more than 24 h, indicating that the biological half-life exceeds the pharmacological half-life [15, 16]. Multiple studies have shown than HCTZ dosing of 25 mg or more had little effect on further blood pressure lowering compared to 25 mg [17, 18, 19•]. A recently published meta-analysis [19•] showed no statistically significant effect on blood pressure for doses of hydrochlorothiazide less than 6.25 mg daily.

Chlorthalidone: this is not a benzothiadiazine class diuretic. It is a thiazide-like drug. The half-life can reach up to 60 h. The long half-life of chlorthalidone is likely due to its very large volume of distribution [10]. In long-term use, it has also been shown to be as effective in lowering diastolic blood pressure with thrice weekly dosing compared to daily dosing; on the other hand, systolic blood pressure was moderately lower using the daily dosing [20]. In one study, 100 mg of chlorthalidone was not superior to 50 mg in reducing blood pressure [21]. Of note, the serum concentration of chlorthalidone after a 100-mg dose was only twice that of a 25-mg dose, indicating a plateau effect of the serum concentration curve [22]. A recently published [19•] meta-analysis showed that little effect on blood pressure was achieved with doses higher than 25 mg daily. It should be noted that all of these cited studies were performed in people with normal renal function. Other studies [20, 23] have similar findings.

One of the questions that remains unanswered is whether observed thiazide and thiazide-like diuretics have similar antihypertensive efficacy within their approved dosing ranges for treating high blood pressure. Likewise, the dose response for adverse effects also needs to be taken into consideration. We will first examine this question in people with relatively normal kidney function before discussing antihypertensive effects in people with CKD.

Clinical Outcomes

The question of potency among the various thiazide and thiazide-like diuretics is frequently examined in the literature. However, there are limited data on head-to-head clinical trials, and there are no studies examining efficacy with a crossover clinical trial design. Thus, we are left with meta-analyses examining the dose response from different studies and evaluating cardiovascular (CV) outcomes between trials. For example, in the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attacks Trial (ALLHAT) study [6], chlorthalidone was superior to enalapril for selected CV endpoints, yet in the second Australian National Blood Pressure Study (ANBP) 2 [24], enalapril was more effective in reducing endpoints compared to HCTZ. Based on their meta-analysis, Dorsch et al. [25] have suggested that patients taking chlorthalidone had fewer CV endpoints compared to patients taking HCTZ. But they also noted that patients taking chlorthalidone had more blood pressure reduction than those taking HCTZ. The difference in blood pressure likely explains the differences in outcome.

In a recent meta-analysis by Peterzan et al. [19•], they analyzed the dose response relationship of selected thiazide and thiazide-like diuretics (hydrochlorothiazide, chlorthalidone, and bendroflumethiazide) on blood pressure, serum potassium and uric acid levels. They showed that different thiazides and thiazide-like diuretics markedly differ by potency, with bendroflumethiazide being the most potent (×18) chlorthalidone (×3), and HCTZ the least (×1) (Table 1). Interestingly, they all shared common efficacy with a near similar maximal reduction of systolic and diastolic blood pressure (Table 1). This suggests that these drugs share a common site and mechanism of action. Moreover, the overall incidence of side effects of these drugs on electrolytes paralleled their net effects on blood pressure.

Blood Pressure-Lowering Effect of Thiazide and Thiazide-Like Diuretics

Thiazide and thiazide-like diuretics exert their diuretic effect by inhibition of the Na+/Cl—cotransporter (NCC) in the renal distal convoluted tubule [10, 11]. In the acute phase this results in a decrease in plasma volume because of natriuresis. In addition, venous return to the heart is decreased, which results in diminished cardiac output and decreased blood pressure [26]. van Brummulem et al. showed that thiazides lower blood pressure after 24 weeks, despite the return of cardiac output to pretreatment level by 12 weeks [22]. Infusion of salt-free dextran during the acute phase of thiazide therapy resulted in return of blood pressure to pretreatment levels [27], but not during the chronic phase [28]. These findings suggest that the late blood pressure-lowering effect of thiazides cannot be explained by volume loss, since accumulation of fluid to pretreatment levels occurs during the chronic phase of maintenance therapy [22]. Also, patients with Gitelman's syndrome who lack a functional NCC have been shown to respond with a decrease in blood pressure when given a thiazide drug [10, 13]. Extra-diuretic effects of thiazides likely explain why thiazides have been shown to have greater antihypertensive effects than loop diuretics [12]. Since

Table 1 Selected thiazide and thiazide-like diuretics: minimal and maximum doses as suggested by Peterzan et al.'s [19•] meta-analysis

Drug	Minimal statistically effective dose	Dose needed to reduce systolic blood pressure by 10 mmHg	Near maximum reduction in systolic blood pressure (dose achieved by)
HCTZ	6.25 mg daily	26.4 mg daily	10.1 mmHg (25 mg)
Chlorthalidone	Unable to determine	8.6 mg daily	15.5 mmHg (25 mg)
Bendroflumethiazide	Unable to determine	1.4 mg daily	14.2 mmHg (5 mg)

diuretics and reduction in cardiac output are unlikely the principal cause of the chronic blood pressure-lowering effect of thiazides, one would conclude that this class of drugs must lower total peripheral resistance via a direct or indirect mechanism. The direct mechanism theory is supported by Aleksandro et al. [29], who demonstrated that thiazides drugs reduce the pressor response to norepinephrine in hypertensive and normotensive subjects. Freis et al. [30] also suggested that chlorothiazide reduces the response of peripheral blood vessels to the vasoconstrictive effect of norepinephrine. In experimental work done by Peterson, the direct vascular effects of thiazides were inhibited by local tetraethylammonium (TEA) administration, which selectively blocks single potassium channels in arterial smooth muscle at low concentration, suggesting a role for potassium channel activation [13] by the thiazide drugs. Recently, Zhu et al. [31] suggested that thiazides attenuate the pressor effects of norepinephrine and angiotensin II by calcium desensitization in smooth muscle cells. Additionally, Colas et al. proposed that methyclothiazide, a thiazide drug, relaxes aortic rings, resulting in endothelium-dependent relaxation due to nitric oxide release [32]. Carbonic anhydrase inhibitors are known to possess vasodilatory effects [33, 34]. Yet, to assume that the effect of thiazides is due to their carbonic anhydrase inhibition is suspect, especially since one of the most potent thiazides, bendroflumethiazide, does not inhibit carbonic anhydrase [33]. As mentioned previously, since thiazide and thiazide-like diuretics have similar antihypertensive efficacy, despite different dose potencies, it suggests they have a common mechanism of site and action.

In summary, there are a number of interesting reports indicating that thiazide and thiazide-like diuretics possess extra-diuretic effects that would be important in lowering blood pressure. These may be of some value in patients with advanced CKD.

Despite the assumption that thiazides are not effective in advanced kidney disease [8, 9], recent evidence showed that 25 mg of hydrochlorothiazide reduced mean blood pressure from 101 to 94 mmHg ($p<0.05$) in patients with stage 4-5 CKD [35••], and in 1979 the Jones et al. trial showed chlorthalidone was effective in reducing blood pressure in patients with advanced CKD [36].

Thiazide and Thiazide-Like Diuretic Use in Advanced CKD

For years it has been assumed that the antihypertensive properties of thiazide and thiazide-like diuretics are tied to their "diuretic" properties. The "reverse whole body autoregulation" mechanism [37] indicated that the initial volume contraction with these drugs resulted in vasoconstriction/reduction in cardiac output mediated by the renin-angiotensin system and sympathetic nervous systems. Over time, vasodilation would ensue, plasma volume would rise, but not back to pre-treatment levels, and cardiac output would return to baseline. Despite these "traditional beliefs," there is evidence that thiazide and thiazide-like diuretics reduce blood pressure in patients with CKD [35••, 36] and have natriuretic effects [35••, 36, 38, 39].

Jones et al. [36] first noted that chlorthalidone effectively lowered blood pressure compared to placebo in patients with CKD in 1979. Knauff et al. [39] later reported that HCTZ alone, or in combination with the loop diuretic, furosemide, facilitated diuresis in patients with CKD, even at a GFR below 30 ml/min/1.73 m^2. Dussol et al. [38] conducted a double-blind, randomized crossover trial involving seven patients with GFR below 40 ml/min/1.73 m^2 in which he compared furosemide to HCTZ with respect to sodium and chloride fractional excretion. The study concluded that HCTZ increased the fractional excretion of sodium and chloride more than furosemide in hypertensive CKD patients and mean arterial blood pressure decreased by the same amount with both diuretic treatments.

More recently, Dussol et al. [35••] conducted a longer duration randomized double-blinded crossover trial (3-month period on each drug and on combination therapy) comparing 60 mg of daily long-acting furosemide to 25 mg daily HCTZ in patients with stage 4-5 CKD to assess the fractional excretion of sodium and chloride after chronic use of the aforementioned drugs. In this trial, 23 hypertensive stage 3-4 CKD patients were randomized to start a 3-month period of either HCTZ or furosemide therapy. This was followed by a washout period, after which patients had furosemide or HCTZ for 3 months. The final phase of the study was an open phase, where all patients received both drugs for a 3-month period. Blood pressure, 24-h measurement of urinary sodium, chloride, potassium, urea, protein and urine volume in addition to

serum electrolytes, BUN, creatinine, calcium, phosphate and uric acid were examined at day 0, day 60, day 90, day 120, day 210, day 240 and day 330. This study demonstrated that both drugs significantly reduced the mean blood pressure ($p<0.05$), but the mean blood pressure decrement did not differ between the HCTZ and the furosemide group. In both groups, HCTZ alone and furosemide alone did not significantly increase the fraction excretion of sodium after the 3-month period. Interestingly, the lack of increase in excretion of sodium was not consistent with what they demonstrated in the shorter pilot study [38]. The authors suggested that this might be due to the new sodium chloride balance achieved at a lower volume status.

The combined regimen of HCTZ and furosemide did significantly increase the fraction excretion of both sodium and chloride at 3 months, and only the combined regimen significantly reduced the GFR, likely because of volume contraction. The mechanisms by which HCTZ might continue to exert its diuretic effect and/or blood pressure-lowering effect in CKD patients might be explained by what Bricker et al. described as the magnification phenomena [40] in renal loss: "The addition or loss from extracellular fluid of any given amount of a substance that is actively regulated by the kidneys will evoke an excretory response per nephron that varies inversely with the number of surviving nephrons." In other words, if a person with normal (100 ml/min/1.73 m^2) GFR ingests 7 g of salt, each nephron must excrete 1/200th of the sodium it filters, whereas if a patient with GFR of 20 ml/min/1.73 m^2 ingested the same amount of salt, each nephron must excrete 1/40 of its filtered load. So if natriuresis is important for blood pressure reduction, then a sufficient diuretic effect is needed to implement this per nephron change. However, how does one explain the comparable antihypertensive effects of HCTZ versus furosemide in CKD patients? Is this a diuretic or extra-diuretic effect?

Conclusion

More studies are needed to examine the physiology of action of thiazide and thiazide-like diuretics in patients with reduced GFR. It is evident in the available, albeit small, clinical literature that these drugs do possess antihypertensive properties even in patients with CKD stage 4. Thus, they do deserve more consideration to help control blood pressure in patients with CKD, perhaps in place of loop diuretics, especially when there is no obvious clinical evidence of volume overload.

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